REMARKS

This Amendment Accompanies a Request for Continued Examination. Claims 1-22 are pending. Claims 6, 9 and 15-17 stand withdrawn as being directed to a non-elected invention. Accordingly, claims 1-5, 7-8, 10-14 and 18-22 are under examination. Claims 1 and 19 have been amended. Support for the amendments can be found throughout the application as filed. Support for the amendment directed to solving the linear optimization problem to provide an optimal solution for the bioengineering objective function that simultaneously requires optimality of the cellular objective function can be found at, for example, paragraphs 0020 and 0038-0043. Accordingly, the amendments do not introduce new matter and entry thereof is respectfully requested.

Entry of the proposed amendments is respectfully submitted to be proper because the amendments are believed to place the claims in condition for allowance.

Applicants acknowledge withdrawal of the rejection of claims 1, 3-5, 7-8, 10-14 and 18-22 under 35 U.S.C. § 101.

Rejections Under 35 U.S.C. § 112

Claims 1-5, 7-8, 10-14 and 18-22 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly being unclear for use of the term "simultaneously." The Examiner alleges that a singular optimization problem is optimized, however, the term "simultaneously" suggests another operation.

Applicants submit that the claims are clear as written. However, to further prosecution Applicants have amended claims 1 and 19 to recite that the linear optimization problem is solved to provide an optimal solution for the bioengineering objective function that simultaneously requires optimality of the cellular objective function. In light of this amendment, Applicants submit that this ground of rejection is moot and respectively request its withdrawal.

Rejections Under 35 U.S.C. § 103

Claims 1, 5, 7, 8, 10, 11, 13, 14 and 19-22 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis et al., *AIChE J.* 42:1277-1292 (1996), in view of Varma et

al., *Biotechnol. and Bioeng.* 42:59-73 (1993) and in view of Bhaskar et al., *Rev. Chem. Eng.* 16:1-54 (2000). The Examiner alleges that the claims fail to recite the coupling of a cellular objective with a bioengineering objective and simultaneously solving for an optimal solution using linear programming.

Applicants respectively disagree. However, claims 1 and 19 have been amended to more explicitly state that the following the step of forming a linear optimization problem that couples the at least one cellular objective function with the at least one bioengineering objective function, the linear optimization problem is solved to provide an optimal solution for the bioengineering objective function that simultaneously requires optimality of the cellular objective function.

The Examiner further alleges that Varma et al. suggests the coupling of objective functions in a linear optimization problem allegedly because the optimal trade off between growth and production is practically linear. Bhaskar et al. is alleged to suggest the simultaneous optimization of several objectives which cannot be compared easily with each other and combined into a single, meaningful scalar objective function and that Pareto surfaces were generated for a three objective function problem.

Applicants respectfully disagree. The claims are directed to forming a linear optimization problem that couples the at least one cellular objective function with the at least one bioengineering objective function and solving the linear optimization problem to provide an optimal solution for the bioengineering objective function that simultaneously requires optimality of the cellular objective function. Hatzimanikatis et al., Varma et al. and Bhaska et al. in combination or together with general knowledge in the art fail to suggest or provide an incentive to one skilled in the art to arrive at the claimed invention with a reasonable expectation of success.

Hatzimanikatis et al. describe solutions to <u>different</u> linear optimization problems. With respect to Varma et al., the computation of an optimal trade-off between growth and metabolite production has been established. However, solving a linear optimization problem to provide an optimal solution for the bioengineering objective function that simultaneously requires optimality of the cellular objective function has not. Although the cited passage at page 72, col. 2, appears to point out that a negative correlation is expected and for most biochemicals the trade-off is

practically linear, the passages at, for example, pages 64 and 67 clearly teach the separate optimization of single objective functions. Hence, the teaching at page 72, col. 2, that "[t]he general conceptual framework presented [in Varma et al.] can be used to obtain a detailed analysis for a particular product as a guide to the development of a bioprocess" is directed to separate optimizations of single objective functions and similarly fails to suggest or provide an incentive to couple different objective functions and simultaneously optimize those different objective functions by linear optimization.

For example, Varma et al. describe:

> We have determined the production capabilities of the *E. coli* metabolic network by incorporating a drain for specific biochemicals in the metabolic network and maximizing them using linear programming. We compute maximal yields of amino acids and nucleotides from three substrates: glucose, glycerol, and acetate.

Id. at page 64, col. 2, first paragraph (emphasis added).

Thus, Varma et al. does no more than solve for a single objective function, maximal yields of amino acids, on each of three different substrates. Each optimization problem is performed separately from the others. This conclusion is further illustrated when Varma et al. describe:

> An optimal trade-off between growth and biochemical production can be assessed by choosing a production rate for a particular product between zero and the maximum production rate and then maximizing the growth rate.

Id. at page 67, col. 2, second paragraph (emphasis added).

Thus, a set value (between zero and maximum rate) is chosen for one function and the second function is optimized separately. There is no coupling of cellular and bioengineering objective functions to simultaneously solve for an optimal solution of each using linear optimization. Accordingly, Varma et al. is cumulative with Hatzimanikatis et al. and fails to suggest or provide an incentive for solving a linear optimization problem to provide an optimal solution for a bioengineering objective function that simultaneously requires optimality of a cellular objective function. Rather, Varma et al. describe choosing a set value for one function and then optimizing the other function.

Bhaskar et al. describe various methods for generating Pareto sets using multiobjective optimization. The various methods fail to suggest or provide an incentive for solving a linear optimization problem to provide an optimal solution for a bioengineering objective function that simultaneously requires optimality of a cellular objective function because the methods of Bhaskar et al. either: 1) arbitrarily assign weights to multiple objective functions prior to solution (parametric), 2) arbitrarily set constraints on secondary objective functions prior to solution (e-constraints), or 3) arbitrarily set goals for multiple objective functions prior to solution that the optimization algorithm tries to match (goal programming). As explained previously of record and reasserted here, requiring optimal solutions for both coupled objective functions using linear programming as is claimed inherently excludes the various approaches taught by Bhaskar et al.

Thus, Hatzimanikatis et al. and Varma et al. independently solve different linear optimization problems, but fail to provide any suggestion or incentive for coupling cellular and bioengineering objectives using a linear optimization problem. Bhaskar et al. employs non-linear programming problems and fail to suggest using a linear optimization problem for simultaneously solving for different objectives to arrive at an optimal solution. Absent some suggestion for forming a linear optimization problem that couples at least one cellular objective function with at least one bioengineering objective function and solving the linear optimization problem to provide an optimal solution for the bioengineering objective function that simultaneously requires optimality of the cellular objective function the cited combination cannot render the invention as claimed obvious. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claims 2, 4 and 18 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis et al., *AIChE J.* 42:1277-1292 (1996), in view of Varma et al., *Biotechnol. and Bioeng.* 42:59-73 (1993) and in view of Bhaskar et al., *Rev. Chem. Eng.* 16:1-54 (2000), and further in view of Yang et al., *Metabolic Engineering* 1:26-34 (1999). Hatzimannikatis et al., Varma et al. and Bhaskar et al. are cited as applied to claims 1, 5, 7, 8, 10, 11, 13, 14 and 19-22 above. Yang et al. is cited for allegedly describing use of a candidate gene to genetically modify an organism. Applicants respectfully submit that the claimed methods are unobvious over the combination of Hatzimanikatis et al., Varma et al., Bhaskar et al. and Yang et al.

As set forth above, Applicants respectfully submit that Hatzimanikatis et al. in combination with Varma et al. and Bhaskar et al. do not teach or suggest the claimed methods.

Furthermore, Applicants respectfully submit that Yang et al. does not cure the deficiencies of the combination of Hatzimanikatis et al., Varma et al. and Bhaskar et al. Yang et al., at best, describe the use of metabolic flux analysis in an *Escherichia coli* strain deficient in the acetate production pathway. However, Yang et al. does not describe or provide any incentive for solving a linear optimization problem to provide an optimal solution for a bioengineering objective function that simultaneously requires optimality of a cellular objective function. Accordingly, Applicants respectfully submit that the claimed methods are unobvious over Hatzimanikatis et al., in combination with Varma et al., Bhaskar et al. and Yang et al. and respectfully request that this rejection be withdrawn.

Claims 1, 5, 7-8, 10-14 and 19-22 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Burgard et al., *Biotechnol. Bioeng.* 74:364-375 (2001), in view of Varma et al., *Biotechnol. and Bioeng.* 42:59-73 (1993) and in view of Bhaskar et al., *Rev. Chem. Eng.* 16:1-54 (2000). Burgard et al. is cited in lieu of Hatzimanikatis et al. in the above rejection of claim 1. Varma et al. and Bhaskar et al. are cited for the same reasons in the above rejection of claim 1.

As set forth above with respect to the rejection of claims 1 and 19 over Hatzimanikatis et al., Varma et al. and Bhaskar et al., Burgard et al., Varma et al. and Bhaska et al. in combination or together with general knowledge in the art fail to suggest or provide an incentive to one skilled in the art to arrive at the claimed invention with a reasonable expectation of success.

Burgard et al. describe solutions to <u>different</u> linear optimization problems. Varma et al. chooses a fixed value for one objective and separately, and iteratively, solves for the second value. Thus, Varma et al. is cumulative with Burgard et al. and both fail to suggest or provide an incentive for solving a linear optimization problem to provide an optimal solution for a bioengineering objective function that simultaneously requires optimality of a cellular objective function. Additionally, the various methods described by Bhaskar et al. fail to suggest or provide an incentive for solving a linear optimization problem to provide an optimal solution for a bioengineering objective function that simultaneously requires optimality of a cellular objective function because the methods of Bhaskar et al. either: 1) arbitrarily assign weights to multiple

objective functions prior to solution (parametric), 2) arbitrarily set constraints on secondary objective functions prior to solution (e-constraints), or 3) arbitrarily set goals for multiple objective functions prior to solution that the optimization algorithm tries to match (goal programming). Absent some suggestion for solving a linear optimization problem to provide an optimal solution for a bioengineering objective function that simultaneously requires optimality of a cellular objective function, the cited combination cannot render the invention as claimed obvious. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claims 1-4 and 18 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Burgard et al., *Biotechnol. Bioeng.* 74:364-375 (2001), in view of Varma et al., *Biotechnol. and Bioeng.* 42:59-73 (1993) and in view of Bhaskar et al., *Rev. Chem. Eng.* 16:1-54 (2000), and further in view of Yang et al., *Metabolic Engineering* 1:26-34 (1999). Burgard et al., Varma et al. and Bhaskar et al. are cited as applied to claims 1, 5, 7, 8, 10-14 and 19-22 above. Yang et al. is cited for allegedly describing use of a candidate gene to genetically modify an organism. Applicants respectfully submit that the claimed methods are unobvious over the combination of Burgard et al., Varma et al., Bhaskar et al. and Yang et al.

As set forth above, Applicants respectfully submit that Burgard et al. in combination with Varma et al. and Bhaskar et al. do not teach or suggest the claimed methods. Furthermore, Applicants respectfully submit that Yang et al. does not cure the deficiencies of the combination of Burgard et al., Varma et al. and Bhaskar et al. Yang et al., at best, describe the use of metabolic flux analysis in an *Escherichia coli* strain deficient in the acetate production pathway. However, Yang et al. does not describe or provide any incentive for solving a linear optimization problem to provide an optimal solution for a bioengineering objective function that simultaneously requires optimality of a cellular objective function. Accordingly, Applicants respectfully submit that the claimed methods are unobvious over Burgard et al., in combination with Varma et al., Bhaskar et al. and Yang et al. and respectfully request that this rejection be withdrawn.

CONCLUSION

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned if there are any questions.

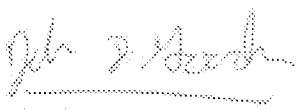
This amendment accompanies the filing of a Request for Continued Examination (RCE). Please charge Deposit Account No. 26-0084 the amount of $405.00 (small) for the RCE per the attached transmittal.

This is a request under the provision of 37 CFR § 1.136(a) to extend the period for filing a response in the above-identified application for three months from October 6, 2010 to January 6, 2011. Applicants are a small entity; therefore, please charge Deposit Account No. 26-0084 in the amount of $555.00 to cover the cost of the three-month extension. Any deficiency or overpayment should be charged or credited to Deposit Account 26-0084.

No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



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